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Endogenous estradiol and progesterone may have important effects on endothelial function in pre-menopausal women and may thereby influence the time course of atherogenesis. This effect may also correlate with changes in exercise and could influence how women perform during times of stress. We studied endothelium-dependent vasodilation of the brachial artery during three phases of the menstrual cycle in 20 eumenorrheic subjects to determine the effect of endogenous estradiol and progesterone. The degree of endothelium-dependent, flow-mediated vasodilation was assessed using high resolution brachial artery ultrasound comparing baseline diameter to that obtained during reactive hyperemia. Endothelium-independent vasodilation was similarly assessed by measuring brachial artery diameter after administration of sublingual nitroglycerin. Exercise performance was measured by determining the maximum oxygen consumption and the endurance time on an anaerobic speed test (AST). Serum lipids were measured along with the estradiol and progesterone levels was also determined. Each subject was studied at three phases of the menstrual cycle: early follicular phase when estradiol and progesterone levels are low, at mid-cycle when estradiol levels are elevated and progesterone levels remain low, and during the luteal phase when levels of both hormones are elevated. Compared to the early follicular and luteal phases, flow-mediated vasodilation was greatest at mid-cycle (follicular 8.0 +/- 1.1%; mid-cycle 10.9 +/- 1.4%, luteal 7.6 +/- 1.1%. p= 0.059). The serum progesterone level was a significant negative correlated of flow-mediated vasodilation (R= -0.261, p=0.027). Lipid levels, maximum oxygen consumption and AST times did not change significantly during the three phases of the menstrual cycle. We conclude that in normal female subjects, endothelium-dependent, flow-mediated vasodilation is enhanced when serum estradiol levels are elevated and unopposed by elevated levels of progesterone, with a similar cyclical trend for endothelium-independent, nitroglycerin-induced vasodilation.

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Table of Contents

Introduction

With increasing numbers of female members of the US Armed Forces, aspects of physical fitness unique to women are increasingly important to military readiness and thus to the success of the overall mission. In addition to the physiologic and psychologic stressors common to all military personnel, female members are also subject to hormonal fluctuations during the course of the female menstrual cycle. There is a growing body of knowledge regarding the effects of estrogens and progestins on a large number of metabolic processes, including carbohydrate (1-4) and lipid metabolism (5), thermoregulation(6), maintenance of extracellular plasma volume(7), ventilation (8), muscle fiber strength (9), maximal aerobic capacity and generalized endurance (10-19). Cyclical changes in strength, generalized endurance and maximal aerobic capacity may be of extreme importance in combat and/or other situations of extreme stress.

There have been a number of studies investigating the effects of the menstrual cycle on various measures of exercise performance (10-19). The results of these studies have been inconsistent, perhaps due to a number of methodological problems. Many early trials failed to document ovulation with hormone levels. Virtually every study has included fewer than 15 subjects and measured numerous outcome variables leading to problems with both Type I and Type II error. Most investigators have studied women during the mid-follicular phase when progesterone and estradiol levels are low and during the mid-luteal phase when progesterone and estradiol levels are elevated, but not at mid-cycle during ovulation when estradiol levels rise while progesterone levels remain low. Since progesterone has many "anti-estrogenic" properties, important physiologic effects of these two hormones may be masked by studying only the mid-follicular and mid-luteal time periods (12).

Recent studies have demonstrated important effects of estrogens on human vascular reactivity (20) which may be important to exercise performance. At times of peak exertion, the peripheral arterioles (resistance vessels) dilate maximally in order to increase overall perfusion by the process of autoregulation. The larger muscular arteries dilate in response to the increased blood flow, a process termed, "flow-mediated vasodilation." Flow-mediated vasodilation is accomplished by the release of a locally acting vasodilator hormone—endothelium-derived relaxing factor or EDRF-- from healthy vascular endothelial cells and this process is termed "endothelium-dependent vasodilation"(21). In the human coronary arteries and peripheral circulation, endothelium-dependent vasodilation is blunted in subjects with established atherosclerosis as well as in those with risk factors for atherosclerosis such as hypercholesterolemia (21-33). In healthy post-menopausal females, the acute administration of intravenous conjugated estrogen leads to enhancement of endothelium-dependent vasodilation (20). It is not known whether the endogenous cycling of estradiol and progesterone produces cyclical changes in endothelium-dependent vasodilation. Furthermore, it is not known whether changes in endothelium-dependent vasodilation correlate with changes in exercise performance. Finally, it is not known whether hypercholesterolemia modulates the cyclical hormonal effects due to blunting of baseline endothelium-dependent vasodilation.

We hypothesize that cyclical changes in estradiol and progesterone during the human female menstrual cycle are associated with changes in endothelium-dependent vasodilation, with the most pronounced vasodilation occurring during the mid-cycle when estradiol is unopposed by progesterone. We also believe that cyclical changes in endothelium-dependent vasodilation will correlate with cyclical changes in exercise performance and serum cholesterol levels.

Methods

Subjects

We recruited 28 eumenorrheic, females on active military duty at Wilford Hall Medical Center, San Antonio, TX. Eumenorrhea was defined as duration of menstrual flow 4 +/- 2 days, cycling at 28 +/- 2 days over the previous 6 months. Eight women originally enrolled in the study were later excluded secondary to not completing all three phases of the study (n=3), incomplete laboratory data (n=1) or inappropriate fluctuations in serum hormone levels (n=4) defined as lack of an estrogen surge at mid-cycle or progesterone surge during the luteal phase. Hence, the final study group consisted of 20 subjects. Exclusion criteria included pregnancy, current use of oral contraceptives, current cigarette use, and the presence of a medical condition that required regular medication. The non-pregnant state was confirmed by urine beta-HCG. All subjects provided written informed consent.

Study Design

Blood sampling, determination of maximum oxygen consumption, endurance time on an anaerobic speed test (AST) and measurement of flow-mediated vasodilation and nitroglycerin-induced dilation were performed at three times during the menstrual cycle: the follicular phase (days 1-3), ovulation (days 11-13) and the luteal phase (days 23-25), with the onset of menses defined as day 0. Serum estradiol and progesterone levels were measured by sensitive radioimmunoassay (estradiol: Tosoh AIA-1200; progesterone: Isodata-520). Lipid profiles were measured using a standard lipid assay (Boehringer-Manheim Hitachi 917).

Flow mediated vasodilation and nitroglycerin-induced dilation were performed using high-resolution ultrasonography. Details of the technique used in our laboratory are published elsewhere (34). Briefly, images were obtained using a Hewlett-Packard 7.5 MHz linear array transducer and a sonos 2500 cardiac ultrasound system with vascular imaging software (Hewlett-Packard, Andover, Massachusetts). After subjects rested quietly for at least 5 minutes, baseline 2-dimensional longitudinal images of the left brachial artery were obtained at a location between 2 and 10 cm above the antecubital fossa. Next a blood pressure cuff placed proximal to the imaging transducer was inflated to suprasystolic pressure for 5 minutes. After rapid deflation of the cuff, flow-mediated vasodilation was assessed by imaging the brachial artery continuously with the transducer maintained at its original location during reactive hyperemia. Subjects rested quietly for 5 minutes, and endothelium-independent vasodilation was assessed after administration of sublingual nitroglycerin spray (0.4 mg). In addition to 2-dimensional imaging, flow

was estimated by continuous wave doppler for each of the scans. All images were recorded on super VHS tape for later analysis. For each subject, a technician blinded to order of the scans identified comparable segments for analysis using anatomic landmarks such as a vessel branchpoint. Three diameter measurements were obtained during each of 3 consecutive cardiac cycles at end-diastole. For the scans during reactive hyperemia, images were selected 60 seconds after release of the blood pressure cuff. The 9 measurements for each scan were averaged for subsequent statistical comparison.

Maximum oxygen consumption was determined using a stationary bicycle at a continuous speed, ramped resistance protocol and an on-line gas analysis system (Sensormetrics). The anaerobic speed test was determined by having subjects run at 8 mph at a 20% grade on a treadmill until fatigue, with the overall time measured in seconds (35). Subjects rested at least 1.5 hours following maximum oxygen consumption determination, prior to the AST determination.

Statistical Analysis

Data obtained during the three phases of the menstrual cycle were analyzed with multivariate repeated-measures ANOVA. Linear regression was used to correlate flow-mediated vasodilation with serum estradiol, progesterone, lipid levels, maximum oxygen consumption and AST. Data are expressed as mean +/- SEM, and a $p < 0.05$ was considered statistically significant. Analyses were performed using Systat 5.2 for Macintosh.

Results

The mean age of the subjects was s 29.3 years (range 21-38). Compared to baseline, doppler estimated flow was increased during reactive hyperemia and after sublingual nitroglycerin for all subjects. Table 1 displays the results of hormone levels, lipid levels, and flow-mediated vasodilation and nitroglycerin-induced dilation. Figure 1 displays results of flow-mediated vasodilation and nitroglycerin-induced dilation for each individual patient. Flow-mediated vasodilation was highest during mid-cycle when estrogen was unopposed and was similar during the follicular and luteal phase ($p = 0.041$). There was a similar trend noted for nitroglycerin-induced dilation, with the most pronounced vasodilation in mid-cycle compared with the follicular phase or the luteal phase ($p = 0.059$). The only significant correlate of flow-mediated vasodilation was the serum progesterone level ($R = -0.261$, $p = 0.27$). Lipid levels, maximum oxygen consumption and AST times did not change significantly during the three phases of the menstrual cycle.

Conclusions

Endothelial function estimated by flow mediated vasodilation of the brachial artery is 36% greater during the estrogen surge at mid-cycle than during the follicular phase when estrogen and progesterone levels are low. When both estrogen and progesterone levels are elevated during the luteal phase, flow-mediated vasodilation is similar to when neither hormone level is elevated during early follicular phase. In

addition, we found a significant negative correlation between progesterone levels and flow mediated vasodilation. Our data suggest a similar cyclical pattern for nitroglycerin-induced vasodilation, a measure of endothelium-independent vasodilation, although the p value was of borderline significance. There was no significant difference in serum lipid levels during the menstrual cycle to explain our findings. Exercise performance also did not appear to differ significantly during the menstrual cycle. These results indicate that cyclic changes in estrogen and progesterone have no effect on exercise performance. However, the lack of variation in performance may reflect the low number of patients which were included in the study or the way in which we assessed physical endurance.

The enhanced release of nitric oxide from endothelial cells is the primary mechanism by which the brachial artery dilates during reactive hyperemia (36). There is good evidence that ovarian hormones modulate endothelial function. In cultured endothelial cells, 17 beta-estradiol enhance the expression of constitutive nitric oxide synthase (37). In rabbits, ovarian hormones have been shown to regulate the unstimulated release of nitric oxide (38). In a dog model, Miller and Vanhoutte showed that progesterone antagonizes the enhanced coronary artery endothelium-dependent vasodilation associated with estrogen administration (39). In observational human study comparing endothelium-dependent vasodilation in postmenopausal women receiving hormone replacement therapy with estrogen alone or combination progesterone and estrogen, the addition of progesterone was associated with 18% lower flow-mediated vasodilation of the brachial artery, although this difference was not significant perhaps due to a small sample size (40). In contrast to the results of this study, Hashimoto and colleagues found that flow-mediated vasodilation is enhanced in human subjects whenever estradiol levels are elevated, regardless of the level of serum progesterone (41).

In addition to effects modulated by the endothelium, estrogen also potentiates endothelium-independent vasorelaxation. For example, Chester and colleagues demonstrated that 17 beta-estradiol directly induces relaxation in atherosclerosis-free human coronary arteries harvested from patients undergoing heart or heart-lung transplantation (42). Another group showed that exogenous estrogen potentiates endothelium-independent vasodilation in subjects with risk factors for vascular dysfunction (43). Hashimoto demonstrated that endothelium-independent vasodilation was augmented in phases of the menstrual cycle associated with elevated estradiol levels. However, in contrast to the results of this study, progesterone did not attenuate this beneficial effect (41).

In summary, our study confirms the findings of previous investigators that endogenous estradiol has a beneficial effect on endothelium-dependent and independent vasorelaxation. However, our data suggest that progesterone antagonizes the beneficial effect of estrogen on vascular reactivity, and this observation may be important in the development of hormone replacement strategies that minimize cardiovascular risk in post-menopausal women.

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Appendex A

FIGURE LEGEND

Values plotted for flow-mediated vasodilation for each subject during three phases of the menstrual cycle.

Appendix B

TABLE 1: Flow-mediated vasodilation, nitroglycerin-induced vasodilation, hormone and lipid levels during three phases of the menstrual cycle

	Follicular	Mid-cycle	Luteal	p value
FMD (%)	8.0±1.1	10.9±1.4	7.6±1.1	0.041
TNG (%)	24.0±1.7	28.2±1.8	23.6±1.6	0.059
Estradiol (pmol/L)	49±4.6	174±26.6	157±14.1	<0.001
Progesterone (nmol/L)	0.7±0.07	0.9±0.16	9.4±1.0	<0.001
LDL-chol (mg/dl)	94.2±5.3	96.3±5.3	91.3±5.4	NS
HDL-chol (mg/dl)	47.2±1.7	49.5±1.7	49.8±2.0	NS
Triglycerides (mg.dl)	67.3±5.8	77.8±9.6	71.6±6.7	NS

Abbreviations

FMD = flow-mediated vasodilation

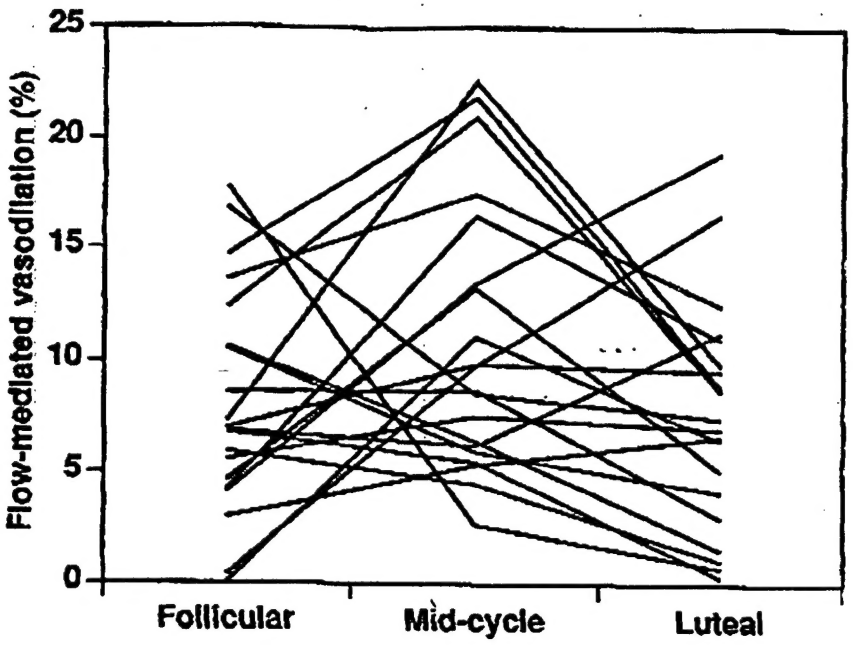
HDL-chol=HDL cholesterol

LDL-chol = LDL-cholesterol

NS = not signficant

TNG = nitroglycerin-induced vasodilation,

Appendix C


Flow-mediated vasodilation (%)
25
20
15
10
5
0
Follicular
Mid-cycle
Luteal